SYNTHESIS OF 2-MERCAPTOBENZTHIAZOLE DERIVATIVES

VI. Reactions of Dihydrothiazolo- and Dihydrothiazino[2, 3-b]Benzothiazolium Salts with some Nucleophilic Reagents*

E. A. Kuznetsova, V. A. Bogolyubskii, L. T. Bogolyubskaya, T. N. Stepanova, and S. V. Zhuravlev

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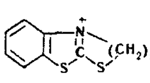
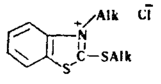
The reactions of 2, 3-dihydrothiazolo- (I) and 2, 3-dihydrothiazino-1, 3-[2, 3-b]benzthiazolium chlorides (II) with water, aqueous sodium hydroxide, aqueous alcoholic ammonia, and hydrazine hydrate are investigated. Excess alcoholic potassium hydroxide cleaves I and II to o-(ω-mercaptoalkylamino)thiophenols, condensation of which with acetyl chloride followed by treatment of the reaction products with potassium iodide gives 2-methyl-3-(ω-mercaptoalkyl)benzthiazolium iodides. A series of dyes is prepared from these compounds.

We previously described a method of preparing 2, 3-dihydrothiazolo- (I) and 2, 3-dihydrothiazino-1, 3-[2, 3-b]benzthiazolium salts (II) [2].



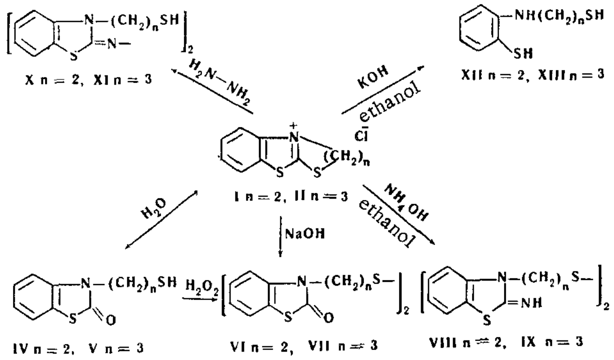
I n = 2, II n = 3

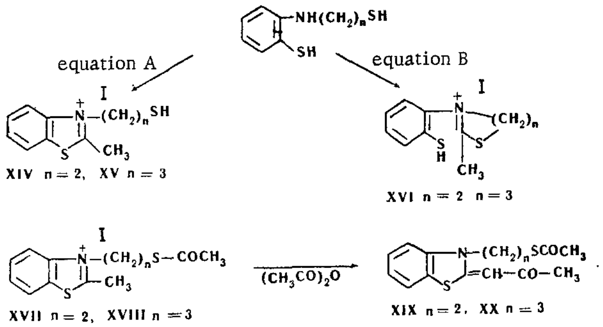


III

The structure of these compounds closely resembles that of 2-alkylmercaptobenzthiazole (III). It might be expected that they would also exhibit closely similar chemical properties. It was first and foremost of interest to investigate nucleophilic substitution. A large positive charge at carbon atom 2 in compound III gives rise to considerable mobility of the alkylmercapto group. Hence treatment of these compounds with cold water or cold aqueous alkalies causes them to readily pass over to the corresponding N-alkylbenzthiazolones [3]; with hydrazine hydrate they form hydrazones or azines [4]; and with quaternary salts of 2-methyl substituted nitrogen ring compounds, or ketomethylene compounds, III gives polymethine dyes [5]. When boiled with excess ethanolic potassium hydroxide, salts of III were cleaved to o-(alkylamino)thiophenols [5] and so on. These reactions are accompanied by splitting off of free alkylmercaptans. It is not difficult to see that reaction of compounds I and II with nucleophilic reagents will not give rise to alkylmercaptans, but the corresponding N-(ω-mercaptoalkyl) derivatives.

In the present paper the reactions of salts I and II with aqueous sodium hydroxide, excess ethanolic potassium hydroxide, ammonia, and hydrazine hydrate are investigated.





Unlike 2, 3, 4, 5-tetrahydrothiazolo[2, 3-b]thiazolium chloride which is hydrolyzed even at room temperature [7], chlorides I and II resist hydrolysis at room temperature for rather a long time. It is of interest to note that a recently synthesized [8] aromatic system of a similar type resists alkaline hydrolysis, and that the UV spectrum of a 0.01 M solution of 3, 5-dimethylthiazolo[2, 3-b]thiazolium perchlorate is unchanged after 18 hr. However heating I and II with water at ~100°–150° C leads to the isolation of compounds giving IR spectra with absorption bands at 2550–2560 cm^{-1} belonging to the SH valence, and at 1665–1670 cm^{-1} belong to the CO valence vibrations in amide. Like ordinary mercapto compounds, compounds IV and V are readily oxidized by oxygen of the air or hydrogen peroxide, to disulfides VI and VII, which we also synthesized by treating I and II with aqueous solutions of sodium hydroxide. In the 1500–1800 cm^{-1} region, the IR spectra of these disulfides are identical with those of IV and V (bands at 1590 and 1665 cm^{-1}, the latter, both for IV and V, assigned to amide C=O), but as was to be expected, no SH absorp-

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*For Part V see [1]

tion bands were observed. Concentrated aqueous ammonia acts like aqueous sodium hydroxide, but in ethanol the final reaction products are the amines VIII and IX, whose IR spectra have a 1500–1800 cm^{-1} region portion differing from the spectra of the preceding compounds. One of the bands, 1665–1670 cm^{-1} and 1612 cm^{-1} (hump) can be assigned to the C=N group, and bands 3220–3225 and 3310 cm^{-1} in VIII and band 3200 cm^{-1} in IX can be assigned to the NH valence.

Due to the high reactivities of chlorides I and II, on the one hand, and that of hydrazine hydrate on the other, it was not possible to stop the reaction at the hydrazone stage, despite change in order of addition, and use of a unit molar ratio of the reactants. Only the azines X and XI, with free mercapto groups, were isolated from the reaction products. The azines showed low solubilities on heating in several organic solvents for them. Their IR spectra showed bands at 2535 and 2475 cm^{-1} for SH, and two bands 1575 and 1600 cm^{-1} in the 1500–1800 cm^{-1} region, one of which can be assigned to C=N valence vibrations, as in the cases of VIII and IX.

Treatment of salts I and II with a 9-fold excess of aqueous alcoholic KOH led to smooth conversion to o-[ω-mercaptoethyl(propyl)amino]thiophenols XII and XIII) which, like all compounds of that type, cause bad dermatoses [6].

The IR spectra of XII and XIII have bands at 2525–2565 cm^{-1} belonging to SH, and bands at 3385 cm^{-1}, belonging to NH. Reaction of XII and XIII with acetyl chloride would be expected to give, as per equation A [9], 2-methyl-3-[ω-mercaptoethyl(propyl)]benzthiazolium salts XIV and XV but the possibility of reaction proceeding as per equation B, to give 2-methyl-3-(o-mercaptophenyl)thiazolium (thiazinium) salts XVI is not excluded. Compounds XII and XIII reacted readily with acetyl chloride to give very hygroscopic chlorides, which were therefore converted to the more stable iodides, which were individual compounds. Heating with anhydrides of carboxylic acids converted them to the corresponding acyl derivatives XVII and XVIII. The IR spectra of compounds XIV and XV had bands at 2415–2430 cm^{-1} belonging to the SH valence, and NH absorption bands were lacking. To finally settle the question of whether reaction proceeds according to equation A or equation B, dimethinemerocyanine dyes were prepared from these salts. As it was found that the presence of mercapto groups greatly decreases solubility of the dyes in ethanol, the same salts obtained from XII and XIII both with a free mercapto group and with an acetylated one, were caused to condense with 3-carbalkoxyamyl-5-acetanilinomethylene-rhodanines [10].

In ethanol solution, all the merocyanines synthesized have absorption maxima at 526–527 nm, very close to the absorption of an ethanol solution of a dimethinemerocyanine with an N-ethylbenzthiazole group (524 nm) [11], while dimethinemerocyanines with an N-ethylazoline group have an absorption maximum at 482 nm [12], and those with an N-ethylthiazine group, one at 495 nm [13]. Thus the reactions of XII and XIII with acetyl chloride proceeded according to equation A, to give salts XIV and XV. Treatment of acetyl derivatives XVII and XVIII with acetic anhydride in the presence of triethylamine gave 2-acetylmethylene-3-(ω-acetylmercaptoethyl)propylbenzthiazolines (XIX and XX).

EXPERIMENTAL

The IR spectra of the compounds were determined by V. S. Troitska and N. D. Solokhina, with a UR-10 instrument, using NaCl and KBr prisms, and thin layers for observation.

N-(β-Mercaptoethyl)benzthiazol-2-one (IV). A solution of 5.5 g (24 mM) I in 50 ml water was heated for 18 hr at 100° C in a sealed tube. The solid was filtered off, yield 2.5 g (60%), mp 48°–49° C (ex aqueous EtOH). Found: C 51.39; 51.15; H 4.30; 4.30; N 6.67; 6.72; S 30.31; 30.34%, calculated for $C_9H_9NOS_2$: C 51.18; H 4.27; N 6.64; S 30.33%.

N-(γ-Mercaptopropyl)benzthiazol-2-one (V). A solution of 11 g (45 mM) II in 30 ml water was heated for 12 hr at 150°–160° C in a sealed tube. The oil was extracted with $CHCl_3$, the extract dried over $MgSO_4$, the solvent taken off, and the residue vacuum distilled, to give 7.2 g (73%) compound bp 165°–166° C (1 mm), n_D^{20} 1.6361. Found: C 53.61; 53.35; H 4.76; 4.99; N 6.59; 6.75; S 28.58; 28.84%, calculated for $C_{10}H_{11}NOS_2$: C 53.33; H 4.89; N 6.22; S 28.44%.

[β-(Benzthiazol-2-on-3-yl)ethyl]disulfide (VI). a) 10 ml 10% H_20_2 was added to a solution of 1.5 g (6.5 mM) IV in 300 ml EtOH, and the whole left overnight at room temperature. The precipitate was filtered off, and washed with water, yield 0.9 g (60%) disulfide, mp 125°–126° C (ex n-PrOH). Found: N 6.52; 6.76; S 30.20; 30.27%, calculated for $C_{18}H_{16}N_2O_2S_4$: N 6.66; S 30.48%.

b) 20 g (85 mM) I was dissolved in 200 ml water, and 12.2 ml 28% NaOH solution added dropwise with stirring. A bulky precipitate separated immediately. This was filtered off and washed with water, yield 12.6 g (70%) VI, mp 125.5°–127° C (ex n-PrOH). Undepressed mixed mp with a specimen prepared as described above.

[γ-Benzthiazol-2-on-3-yl)propyl]disulfide (VII). a) Prepared similarly to the above, using 2.85 g (12.5 mM) IV and 18 ml 10% H_20_2, yield 1.3 g (45%) disulfide mp 93°–94° C (ex EtOH). Found: C 53.31; 53.16; H 4.35; 4.42; N 6.41; 6.44; S 28.36; 28.49%, calculated for $C_{20}H_{20}N_2O_2S_4$: C 53.57; H 4.47; N 6.25; S 28.57%.

b) 3 g (12.3 mM) II was dissolved in 125 ml water, and 3 ml 17% NaOH solution added dropwise, with stirring. Yield 1.15 g (40%) mp 90°–92° C (ex EtOH). Undepressed mixed mp with a specimen prepared as above.

[β-(2-Iminobenzthiazolon-3-yl)ethyl]disulfide (VIII). 45 ml concentrated ammonia solution was added in portions, with shaking, to a solution of 1 g (4.3 mM) I in 100 ml EtOH, until a slight turbidity appeared. The mixture was then left for about 12 hr, when a precipitate formed. A further 35 ml concentrated ammonia solution was added to the solution, and the whole left for about 12 hr. The precipitate was filtered off and washed with EtOH, yield 0.5 g (55%), mp 163°–164° C (ex EtOH). Found: N 13.76; 13.48; S 30.47; 30.68%, calculated for $C_{18}H_{18}N_4S_4$: N 13.39; S 30.63%.

[γ-(2-Imino-benzthiazolon-3-yl)propyl]disulfide (IX). Prepared similarly to VIII, from 1 g II, after 3–4 days standing at room temperature, yield 0.7 g (63%), mp 107°–108.5° C (ex toluene). Found: N 12.37; 12.45; S 28.90; 28.78%, calculated for $C_{20}H_{22}N_4S_4$: N 12.55; S 28.70%.

N-(β-Mercaptoethyl)benzthiazol-2-one azine (X). 5 g (0.1 mole) 80% Hydrazine hydrate was added dropwise, with stirring, to a solution of 11.5 g (0.05 mole) I in 150 ml water. A white precipitate immediately formed and was filtered off. The solid liquified on the filter to a viscous oil (9.1 g) which was crystallized from $CHCl_3$. Found: N 13.44; 13.51; S 30.60; 30.58%, calculated for $C_{18}H_{16}N_4S_4$: N 13.46; S 30.77%.

N-(γ-Mercaptopropyl)benzthiazol-2-one azine (XI). Prepared similarly to X, from 6.05 g (0.025 mole) II, giving 6 g oily material which solidified on boiling with benzene, yield 2 g (36%), mp 188°–189° C (ex benzene). Found: N 12.61; 12.51; S 28.26; 28.23%, calculated for $C_{20}H_{22}N_4S_4$: N 12.68; S 28.83%.

o-(β-Mercaptoethylamino)thiophenol (XII). A solution of 25.2 g (0.45 mole) KOH in 75 ml EtOH was added to a suspension of 11.5 g (0.05 mole) I in 50 ml EtOH. The mixture was refluxed for 1 hr, cooled, the inorganic salts filtered off, and washed on the filter with 10 ml EtOH. The EtOH was distilled off, the residue dissolved in 25 ml water, and neutralized with conc HCl, with cooling. The oil thrown out was extracted with benzene, the benzene solution dried over $MgSO_4$, the solvent distilled off, and the residue distilled, to give 4.7 g (50%) yellow oil, bp 152°–154° C (2 mm). Found: N 7.53; 7.59; S 34.60; 34.31%, calculated for $C_8H_{11}NS_2$: N 7.56; S 34.59%.

o-(γ-Mercaptopropylamino)thiophenol (XIII). Prepared similarly to XII, from 12.5 g II, yield 5.1 g (52%), yellowish oil, bp 158°–160°C (2 mm). Found: N 7.27; 7.16%, calculated for $C_9H_{13}NS_2$: N 7.06%.

N-(β-Mercaptoethyl)-2-methylbenzthiazolium iodide (XIV). A solution of 1.6 g (0.02 mole) acetyl chloride in 5 ml benzene was added to a solution of 3.7 g (0.02 mole) XII in 5 ml benzene. The mixture evolved much heat, and suddenly an oil came out. After cooling the benzene was poured off, the oil washed with 10 ml dry acetone, and dissolved in 10 ml water. 3.5 g KI in 3 ml water was added to the aqueous solution, and the precipitate formed filtered off, then washed with water and acetone. Yield 4.85 g (64.5%), mp 188°–190° C (ex EtOH). Found: N 4.31; 4.37; S 19.21; 19.20; I 37.36; 37.50%, calculated for $C_{10}H_{12}INS_2$: N 4.15; S 18.95; I 37.60%.

N-(γ-Mercaptopropyl)-2-methylbenzthiazolium iodide (XV). Prepared similarly to **XIV** using 4 g (0.02 mole) XIII. Yield 5.15 g (59%), mp 168°–169° C (ex EtOH). Found: N 4.24; 4.04; S 18.36; 18.37; I 35.92; 35.98%, calculated for $C_{11}H_{14}INS_2$: N 3.93; S 18.25; I 36.12%.

N-(β-Acetylmercaptoethyl)-2-methylbenzthiazolium iodide (XVII). A suspension of 1 g XIV in 5 ml Ac_2O was heated for 1 hr at 100° C. The crystals were filtered off, then washed with EtOH and ether. Yield 0.93 g (83%), mp 199°–200° C (ex EtOH). Found: N 3.69; 3.87%, calculated for $C_{12}H_{14}INOS_2$: N 3.69%.

N-(β-Acetylmercaptopropyl)-2-methylbenzthiazolium iodide (XVIII). Prepared similarly to XVII, from 1 g XV, yield 0.7 g (62%), mp 154°–155° C (ex EtOH). Found: N 3.73; 3.72%, calculated for $C_{13}H_{16}INOS_2$: N 3.58%.

N-(β-Propionylmercaptoethyl)-2-methylbenzthiazolium iodide. A suspension of 1 g XIV in 5 ml propionic anhydride was heated for 1 hr at 100° C. Yield 0.7 g (62%), mp 105°–107° C (ex EtOH). Found: N 3.56; 3.57%, calculated for $C_{13}H_{16}INOS_2$: N 3.58%.

N-(γ-Propionylmercaptopropyl)-2-methylbenzthiazolium iodide. Prepared similarly to the above, from 0.5 g XV, yield 0.36 g (62%), mp 144°–145° C (ex EtOH). Found: N 3.52; 3.50%, calculated for $C_{14}H_{18}INOS_2$: N 3.45%.

2-Acetylmethylene-3-acetylmercaptoethylbenzthiazoline (XIX). A mixture of 1.25 g (5 mM) XVII, 4 ml Ac_2O, and 0.7 ml Et_3N was heated on a steam bath for 2 hr. The solvent was taken off, 2.6 ml dil HCl (1:4) added to the residue, the solid filtered off, washed with 7 ml of the same acid (1:4), then with 2 ml water, and suspended in 7 ml water. A solution of $NaHCO_3$ was added to the suspension until it was slightly alkaline. The solid was filtered off, and washed with water, yield 0.85 g (58.6%), mp 211°–212° C. (The product was purified by chromatographing in benzene on alumina.) Yield 0.6 g, mp 213°–214° C. Found: N 4.75; 4.83%, calculated for $C_{13}H_{15}NO_2S_2$: N 4.97%.

2-Acetylmethylene-3-acetylmercaptopropylbenzthiazoline (XX). This was prepared similarly to **XIX**, yield 55.1%, mp 109°–110° C (after chromatographing on alumina). Found: N 4.50; 4.45%, calculated for $C_{15}H_{17}NO_2S_2$: N 4.55%.

3-(ε-Carbethoxyamyl)-5-(3'-mercaptopropylbenzthiazolinyliden-2'-ethylidene)thiazolidin-2-thion-4-one. 0.14 ml Et_3N was added to a warm solution of 0.35 g (1 mM) XV and 0.4 g (1 mM) 3-(ω-carbethoxyamyl)-5-acetanilinomethylenerhodanine (XXI) in 20 ml absolute EtOH, the mixture heated on a steam bath for 1 hr, the products left overnight, and the dye filtered off and washed with EtOH. Yield 0.25 g (50%) substance mp 85°–87° C, from which was obtained 0.2 g pure dye mp 93°–94° C (ex EtOH). Absorption maximum of an EtOH solution at 527 nm. Found: N 5.71; 5.81%, calculated for $C_{23}H_{28}N_2O_3S_4$: N 5.63%.

3-(β-Carbisopropyloxyamyl)-5-(3'-mercaptoethylbenzthiazolinylidene-2'-ethylidene)thiazolidin-2-thione-4-one. Prepared similarly from XIV and 3-(ε-carbisopropyloxyamyl)-5-acetanilinomethylenerhodanine (XXII). Yield of pure dye 18%, mp 131°–132° C (ex EtOH). Absorption maximum of an EtOH solution at 527 nm. Found: N 5.72; 5.77%, calculated for $C_{29}H_{28}N_2O_3S_4$: N 5.63%.

3-(ε-Carbisopropyloxyamyl)-5-(3'-acetylmercaptoethylbenzthiazolinylidene-2'-ethylidene)thiazolidin-2-thion-4-one. Prepared similarly from **XIX** and **XXII**, yield 0.38 g dye mp 126°–127° C (ex EtOH). Absorption maximum of EtOH solution at 526 nm. Found: N 5.03; 4.99%, calculated for $C_{25}H_{30}N_2O_4S_4$: N 5.18%.

3-(ε-Carbethoxyamyl)-5-(3'-acetylmercaptopropylbenzthiazolinyliden-2'-ethylidene)thiazolidin-2-thion-4-one. Prepared similarly from **XX** and **XXI**, yield 88.8%, mp 109°–110° C (ex EtOH). Absorption maximum of an EtOH solution at 527 nm. Found: N 5.26; 5.16%, calculated for $C_{25}H_{30}N_2O_4S_4$: N 5.18%.

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Institute of Pharmacology and
Chemotherapy, AMS USSR,
Moscow

Shostka Branch of the All-Union
Cinematography Scientific Research Institute, Shostka